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Factors associated with dizygotic twinning after IVF treatment with double embryo transfer

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Managed Problem Solving for Antiretroviral Therapy Adherence

A Randomized Trial

Robert Gross, MD, MSCE; Scarlett L. Bellamy, ScD; Jennifer Chapman, MPH; Xiaoyan Han, MS; Jacqueline O'Duor, MSW; Steven C. Palmer, PhD; Peter S. Houts, PhD; James C. Coyne, PhD; Brian L. Strom, MD, MPH

Background: Adherence to antiretroviral therapy is critical to successful treatment of human immunodeficiency virus (HIV). Few interventions have been demonstrated to improve both adherence and virologic outcomes. We sought to determine whether an intervention derived from problem solving theory, Managed Problem Solving (MAPS), would improve antiretroviral outcomes.

Methods: We conducted a randomized investigator blind trial of MAPS compared with usual care in HIV-1 infected individuals at 3 HIV clinics in Philadelphia, Pennsylvania. Eligible patients had plasma HIV-1 viral loads greater than 1000 copies/mL and were initiating or changing therapy. Managed Problem Solving consists of 4 in-person and 12 telephone-based meetings with a trained interventionist, then monthly follow-up calls for a year. Primary outcome was medication adherence measured using electronic monitors, summarized as fraction of doses taken quarterly over 1 year. Secondary outcome was undetectable HIV viral load over 1 year. We assessed 218 for eligibility, with 190 eligible and 180 enrolled, 91 randomized to MAPS and 89 to usual care. Fifty-six participants were lost to follow-up: 33 in the MAPS group and 23 in usual care group.

Results: In primary intention-to-treat analyses, the odds of being in a higher adherence category was 1.78 (95% CI, 1.07-2.96) times greater for MAPS than usual care. In secondary analyses, the odds of an undetectable viral load was 1.48 (95% CI, 0.94-2.31) times greater for MAPS than usual care. In as-treated analyses, the effect of MAPS was stronger for both outcomes. There was neither a difference by prior treatment status nor change in effect over time.

Conclusions: Managed Problem Solving is an effective antiretroviral adherence intervention over the first year with a new regimen. It was equally effective at improving adherence in treatment experienced and naïve patients and did not lose effect over time. Implementation of MAPS should be strongly considered where resources are available.

Trial Registration: clinicaltrials.gov Identifier: NCT00130273

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ADHERENCE TO PHARMACOTHERAPY is key to preventing progression of treatable chronic diseases. Unfortunately, clinically significant nonadherence is common in diabetes mellitus,¹ hypertension,² hypercholesterolemia,³ and human immunodeficiency virus (HIV),⁴ for example. Adherence barriers include depression,⁵ substance abuse,⁶ regimen complexity,⁷ poor social support,⁸ and low health literacy,^{9,10} among others. Adherence interventions have had limited effects, which often wane over subsequent months.¹¹⁻¹³

Patients may have multiple adherence barriers, and so personalized strategies addressing multiple barriers hold the greatest promise for success. We developed Managed Problem Solving (MAPS) to address

barriers to chronic pharmacotherapy adherence. It derives from Problem Solving Therapy (PST), an effective intervention for depression.¹⁴ Problem Solving Therapy trains individuals in generalizable problem-solving skills including identification of difficulties, generation of solutions, and

See Invited Commentary at end of article

evaluation of outcomes.¹⁵ It has been adapted to address coping with cancer and schizophrenia, family caregiving, and family relationships.¹⁶⁻¹⁸ Managed Problem Solving differs from PST; the participant is not trained to become a better generalized problem solver per se. Rather, the interventionist and participant work together to

Author Affiliations are listed at the end of this article.

solve specific adherence barriers using the Problem Solving framework. An overlap with PST is starting with small, achievable goals to ensure success and establish credibility. Notably, MAPS does address some problems that patients believe are important but are only indirectly related to medication adherence. This may reduce stressors that interfere with adherence and encourage continued participation.

We assessed whether MAPS resulted in better adherence to therapy for HIV than usual care. We chose antiretroviral therapy because the relationship between adherence and outcome was well described,¹⁹⁻²² as were the ensuing consequences of disease progression,²³ further HIV transmission,²⁴ and emergence of resistance.²⁵

METHODS

ETHICS STATEMENT

The study was approved by the committee on human subjects research of the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center. All participants provided informed consent and were compensated \$30 per data collection visit, but not intervention visits, for a total of \$270 if all visits were completed. A data and safety monitoring committee reviewed severe intervention-related adverse events (eg, suicidality). There were no early stopping rules.

STUDY SETTING AND PARTICIPANTS

We conducted a randomized investigator-blind trial comparing MAPS with usual care in HIV-1 infected individuals. Recruitment was facilitated by flyers in the clinics and weekly querying of pharmacists and prescribers regarding potential patients at the 2 HIV clinics in the University of Pennsylvania Health System and the HIV clinic at the Philadelphia Veterans Administration Medical Center. Usual care included meeting with a pharmacist for regimen education and, if desired, provision of pill organizers.

Inclusion criteria were at least 18 years old, with HIV-1 plasma viral load greater than 1000 copies/mL, and were treatment naïve and initiating a standard regimen, or treatment experienced and either (1) restarting their most recent suppressive regimen after more than 3 months off or (2) initiating a new regimen with 3 new antiretrovirals with resistance profiles different from their initial regimen or fully susceptible on an HIV resistance assay. After study initiation, we expanded criteria to include regimens with at least 2 fully active and 1 partially active drug based on a resistance assay. Treatment responses for this subpopulation were expected to be sufficiently similar to those for fully active regimens to allow for valid conclusions regarding the effect of the intervention on virologic outcome.²⁶ Exclusion criteria were inability to consent and residence in a setting with automatic medication delivery.

Permuted block randomization with 1:1 allocation was performed in random block sizes of 6 to 9 individuals. The biostatistician generated a randomization list by computer and placed assignments into sealed security envelopes numbered sequentially and maintained in a locked drawer by the study coordinator. At enrollment, the study coordinator selected the next envelope, which was opened only after consent. The investigators were blinded by prohibiting their access to the data and contact with participants.

INTERVENTIONISTS AND INTERVENTION

Interventionists were required to have a college degree and some prior experience working with a patient population. We trained 3 interventionists during the trial with 15 hours of training covering essentials of HIV management; behavioral science topics, including depression and substance abuse; and the MAPS manual (available online at <http://www.med.upenn.edu/ccceb/maps-form.shtml>).

Managed Problem Solving consisted of a 5-step process of identifying participants' barriers to adherence, brainstorming for potential solutions, selecting the best option, monitoring its implementation and whether the participant considered the implementation useful, and the participant's adherence. Unsuccessful plans were revised repeating the process. These activities were iterated over the first 3 months until an effective solution was chosen or no further options could be generated. Baseline screening aided in identifying common potential adherence barriers, using Center for Epidemiologic Studies Depression Scale for depressive symptoms,²⁷ the Alcohol Use Disorders Identification Test²⁸ and Addiction Severity Index questionnaires²⁹ for substance abuse, and a questionnaire regarding HIV knowledge, health, and religious beliefs.

The first session began with education concerning the prescribed regimen, medication adherence expectations, common regimen adverse effects, and medication misperceptions (eg, "if you drink alcohol, do not take medications that day"). Problem solving addressed (1) daily routines and daily cues, (2) memory and cognitive aids for pill taking and prescription refills, and (3) identifying and using social supports as encouragement. Depression, substance use or abuse, toxicity management, and competing demands were addressed when screening uncovered these potential barriers. In addition, the interventionist asked open-ended questions for participants to identify additional barriers.

The MAPS participants met with the interventionist within 2 weeks of initiating therapy for approximately 60 to 90 minutes. Three monthly follow-up meetings lasted approximately 20 to 45 minutes. Follow-ups included displaying a calendar plot of the prior month's adherence generated by the electronic monitor. During the first 3 months, weekly telephone calls reinforced the in-person sessions and allowed for problem solving of new issues. Monthly telephone calls for the subsequent 9 months reminded patients about obtaining refills and encouraged continuing the adherence strategies.

Prior to working with study patients, mock sessions were repeated until the interventionist was considered proficient by the investigators. Subsequently, trained staff assessed fidelity on 25 randomly selected intervention session audio tapes. Fidelity was scored using a 21-item tool developed for the protocol with scores ranging from 0 to 100; higher values indicated greater fidelity and a score higher than 50 was considered adequate. More details can be found in the MAPS manual.

OUTCOMES

The primary outcome was antiretroviral adherence, measured using electronic monitors in all participants (Medication Event Monitoring System [MEMS], AARDEX), with each bottle opening considered a dose-taking event. Prospective participants planning to use a pill organizer were required to agree to maintain 1 medication in the MEMS monitored bottle (ie, outside of the pill box). For patients receiving multiple antiretroviral drugs, an algorithm selected the monitored drug in the following order of preference: (1) nonnucleoside analog reverse transcriptase inhibitor (NNRTI), (2) protease inhibitor (ritonavir first), (3) integrase inhibitor, (4) entry inhibitor, or (5) nucleoside reverse transcriptase inhibitors (NRTI).

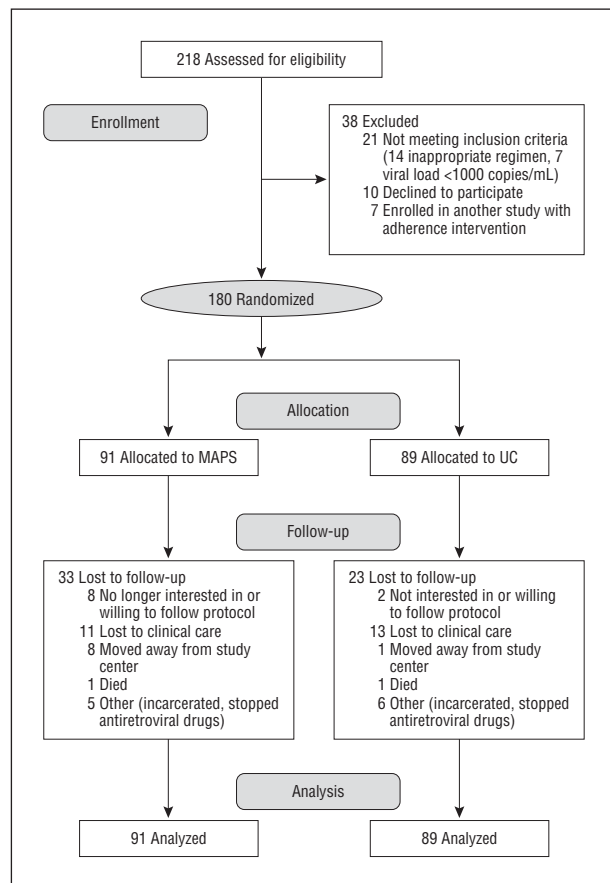


Figure 1. Participant flowchart. MAPS indicates Managed Problem Solving; UC, usual care.

We summarized adherence as fraction of prescribed number of doses taken over each quarter for a year, ranging from 0 to 1. The secondary outcome was undetectable plasma HIV viral load (UDVL), using a lower limit of 75 copies/mL and measured quarterly for a year (Versant, HIV-1 RNA version 3.0, Bayer Corp). These data were collected identically for each group during 9 follow-up visits with the study coordinator over the year.

STATISTICAL ANALYSIS

The primary analysis used an “intention to treat” approach. To be most conservative, missing values were assigned a value of zero adherence. Fraction of doses taken was categorized as 0.70 or less, more than 0.70 to 0.80, more than 0.80 to 0.90, more than 0.90 to 0.95, and more than 0.95. Generalized estimating equations (GEE) with ordinal regression were used to estimate the association between study group and adherence over all 4 quarters of the year.³⁰ In secondary analyses, we tested for potential confounding by measured variables by including covariates in the GEE models and inspecting for changes in the point estimate of the relation between study group and outcome.

Analyses of viral suppression were identical to those of adherence except using logistic regression.³⁰ In secondary “as treated” analyses, missing adherence and viral load data were ignored. In additional analyses, we assessed whether the effect of the intervention varied over time by including treatment group by time interactions in the models.

Finally, we assessed the relation between adherence (independent variable) and virologic suppression (dependent variable) again using GEEs with logistic regression and including missing viral load as detectable.

Table 1. Baseline Characteristics by Study Group

Characteristic	No. (%)	
	MAPS (n = 91)	UC (n = 89)
Age, median (range), y	43 (20-65)	42 (19-60)
Male sex	52 (57)	56 (63)
Race		
Black	80 (88)	73 (82)
White	9 (10)	15 (17)
Other	2 (2)	1 (1)
History of injection drug use	16 (18)	12 (14)
Current drug use	21 (23)	27 (30)
Hazardous alcohol use	14 (15)	18 (21)
Unemployed	73 (85)	69 (78)
Yearly income <\$5000	24 (28)	33 (36)
Treatment naïve	40 (44)	32 (36)
Once-daily regimen	59 (65)	58 (65)
Pills per regimen, median (25th-75th quartiles), No.	3 (1-5)	3 (3-5)
Baseline viral load, log ₁₀ copies/mL, median (25th-75th quartiles)	3.24 (2.46-4.32)	3.47 (2.35-4.40)
Baseline CD4 count cells/mm ³ , median (25th-75th quartiles)	287 (146-370)	244 (116-379)

Abbreviations: MAPS, Managed Problem Solving; UC, usual care.

SAMPLE SIZE

The planned sample size was 200 individuals to achieve greater than 80% power to detect a less than 10% difference in adherence between MAPS and usual care, ignoring the contribution of multiple outcome time points per individual. Recruitment was slower than expected, and the target was decreased to 180 to achieve 80% power to detect a 10% difference in adherence.

RESULTS

ENROLLMENT AND BASELINE CHARACTERISTICS

From September 2005 through February 2010, 218 individuals were referred for participation, with 190 eligible and 180 randomized (95%) (**Figure 1**). Of those enrolled, 91 were randomized to MAPS and 89 to usual care. After the target of 180 was reached, enrollment was closed and follow-up extended until February 2011.

Participants' characteristics are displayed in **Table 1**. Of the 180 participants, 136 (76%) were receiving 3 drug regimens with 2 NRTIs and a boosted protease inhibitor (PI) or an NNRTI (**Table 2**). The remainder were receiving various combinations of up to 6 drugs with the most commonly used NRTI combination being tenofovir and emtricitabine in 88 (49%).

Dropouts occurred for 33 (36%) in the MAPS group and 23 (26%) in the usual care group ($\chi^2 = 2.28$; $P = .13$). The MAPS participants dropped out more commonly for “not wanting to follow the protocol” and moving too far away to follow-up at the site. Other reasons were similar between groups. Fidelity to MAPS was high with a mean (SD) score of 82 (6) points (range, 67-90 points).

ADHERENCE RESULTS BY STUDY GROUP

The proportion of individuals in each adherence category in the MAPS and usual care groups during each quarter is displayed in **Figure 2**. In the primary analysis, the odds of being in a higher adherence category at any follow-up point was 1.78 (95% CI, 1.07-2.96) times greater for MAPS than usual care. Likewise, in the secondary analysis using an as-treated approach, the odds of being in a higher category of adherence at any follow-up point was 2.33 (95% CI, 1.35-4.05) times greater for MAPS than usual care. In further secondary analyses controlling for age, race, sex, treatment-naïve status, use of efavirenz in regimen, baseline viral load, and baseline CD4 cell count, there was no confounding of the relation between study group and adherence outcome. There was no evidence that MAPS' adherence effect differed over time—the study group by time interaction was neither statistically nor clinically significant (data not shown).

VIROLOGIC RESULTS BY STUDY GROUP

In the intention-to-treat analysis of virologic suppression, the odds of having an undetectable viral load at any follow-up point was 1.48 (95% CI, 0.94-2.31) times greater for MAPS than for usual care. Likewise, in the as-treated analyses, the odds of having an undetectable viral load at any follow-up point was 1.98 (95% CI, 1.15-3.41) times greater for MAPS than usual care. At all time points, virologic suppression rates for MAPS exceeded those of usual care (**Table 3**). Again, there was no clear change in the relation between study group and undetectable viral load over time. In further formal analyses, there was no evidence that MAPS' effect on virologic suppression differed over time—the study group by time interaction was neither statistically nor clinically significant (data not shown).

EFFECT OF ADHERENCE ON VIROLOGIC SUPPRESSION

As expected, there was a strong relation between adherence and treatment response. In the analyses where missing viral loads were imputed as "detectable," for every 25% increase in proportion of doses taken, the odds of having an undetectable viral load nearly doubled (odds ratio [OR], 1.99 [95% CI, 1.64-2.41]). In the analyses where missing viral load was left missing, the odds of undetectable viral load for every 25% increase in doses taken was more than double (OR, 2.41 [95% CI, 1.91-3.02]).

OTHER FACTORS ASSOCIATED WITH ADHERENCE AND VIROLOGIC RESPONSE

Treatment-experienced individuals were 0.48 (95% CI, 0.29-0.81) times as likely to be in a higher adherence category and 0.48 (95% CI, 0.30-0.76) times as likely to have undetectable viral loads than treatment-naïve individuals. Higher baseline viral load was associated with a lower likelihood of virologic suppression. For every 1 log₁₀ higher baseline viral load, the odds of having an undetectable viral load was 0.80 (95% CI, 0.65-0.99). Neither of these relationships differed by study group.

Table 2. Index Antiretroviral at Randomization by Study Group

Index Drug	Patients, No.	Study Group, No.	
		MAPS	Usual Care
Atazanavir, ritonavir boosted	64	32	32
Efavirenz	48	30	18
Darunavir, ritonavir boosted	31	15	16
Lopinavir, ritonavir boosted	18	6	12
Fosamprenvir, ritonavir boosted	7	4	3
Raltegravir	4	2	2
Nelfinavir	2	1	1
Nevirapine	2	0	2
Tipranavir, ritonavir boosted	1	1	0

Abbreviation: MAPS, Managed Problem Solving.

COMMENT

This randomized trial of MAPS demonstrated that it is effective at improving adherence over the first year of a new antiretroviral regimen in a population with relatively high rates of nonadherence. We found no evidence that MAPS was less effective in individuals with prior treatment experience despite those individuals being at higher risk of nonadherence. It did not lose effect over time. The impact of this increased adherence was borne out by the higher proportion of individuals with undetectable viral loads. This effect too persisted for the entire treatment period.

Numerous strategies to improve pharmacotherapy adherence have been tested, particularly for antiretroviral therapy.¹² Results have mostly been disappointing, with only a few strategies showing benefits for both adherence and virologic response.^{31,32} Directly observed therapy (DOT) has been the most intensively studied, but, in unselected populations, has not been associated with important³³ or sustained benefits.³⁴ However, some evidence suggests that DOT might be useful in select subpopulations, such as active substance abusers.³⁵ Technological interventions have had mixed results with text messages showing benefit in a developing world setting,³² but not in the developed world.³⁶ Behavioral strategies have also had mixed success. Simple financial incentives for adherence have had some effect while continued, but not consistently, and typically wane when the financial reward is stopped.³⁷ Feedback regarding adherence has been used successfully previously, but in a population excluding ethnic minorities, substance abusers, and the mentally ill.³¹ Problem solving has been incorporated into larger intervention packages but not studied on its own.³⁸ Use of multiple modalities to improve adherence has been suggested for years, but relatively little evidence to date has been generated. Notably, MAPS incorporates both a behavioral strategy and technology—the adherence feedback is generated via electronic monitors.

Managed Problem Solving is relatively resource intensive, but such strategies can be presumed to be cost-effective if they cost less than \$1000 per year per participant for a 10% increase in adherence.³⁹ Although we

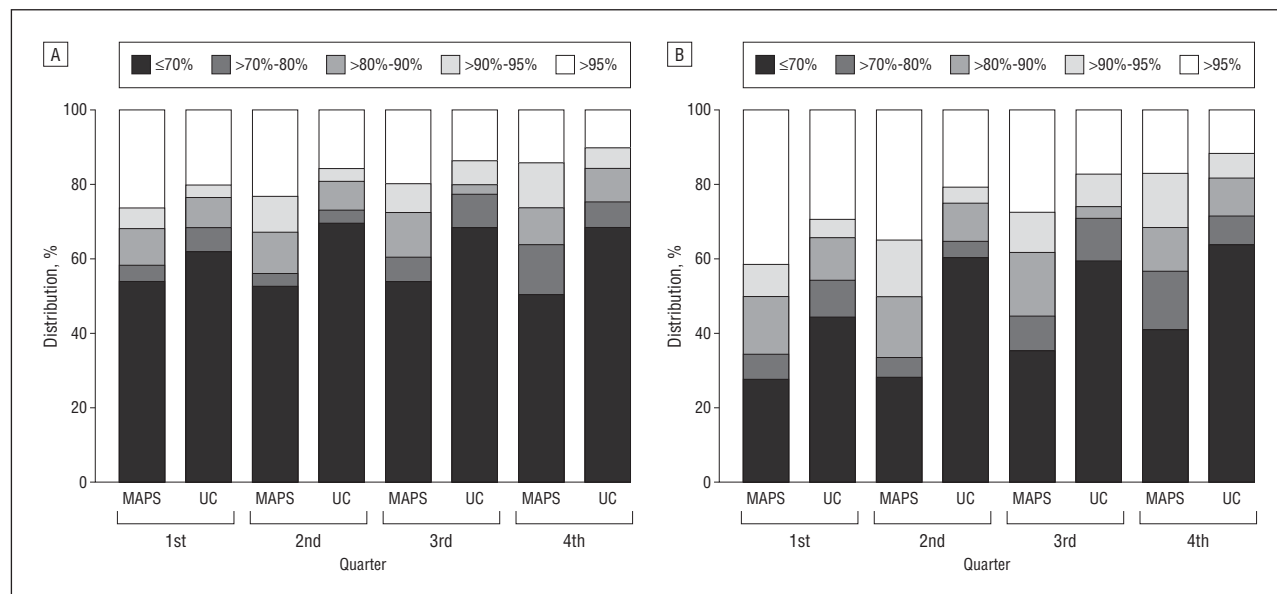


Figure 2. Longitudinal distribution of adherence categories. A, Intent-to-treat. B, Categories, as treated. MAPS indicates Managed Problem Solving; UC, usual care.

Table 3. Virologic Response Rates per Quarter by Study Group

Proportion With UDVL	Study Group, No. (%)	
	MAPS	Usual Care
Missing = failure ^a		
Q1	53 of 91 (58)	42 of 89 (47)
Q2	53 of 91 (58)	47 of 89 (53)
Q3	52 of 91 (57)	39 of 89 (44)
Q4	54 of 91 (59)	45 of 89 (51)
Missing = missing ^b		
Q1	53 of 68 (78)	42 of 67 (63)
Q2	53 of 62 (86)	47 of 70 (67)
Q3	52 of 69 (75)	39 of 59 (66)
Q4	54 of 72 (75)	45 of 76 (59)

Abbreviations: MAPS, managed problem solving; UDVL, undetectable plasma human immunodeficiency virus viral load.

^aMissing data were analyzed as failure.

^bMissing data were ignored in analysis.

did not perform a formal cost-effectiveness analysis, we estimate that approximately 20 participants were followed per year by an interventionist committing 15% effort at a salary of approximately \$50 000 per year. Including approximately \$150 per electronic monitor per participant, the cost for such an activity is substantially less than \$1000 per year.

There are several potential limitations to this study. First, although it was a randomized trial, participants could not be blinded to study arm. However, since the treatment was crucial to their health, it is unlikely that their awareness of study arm had an impact on their behavior outside of the interaction with the interventionist. In fact, it is possible that adherence in the control arm was better than would be expected in this population since this condition provided extra visits with the study coordinator, who paid more attention to their medication taking. Second, participants were recruited from academic spe-

cialty HIV clinics where services for adherence may be greater than those in general medical clinics. If so, the effect of MAPS may be even greater in less resourced settings. Third, it is unclear how the dropouts truly affected the results. Although both the intention-to-treat and as-treated analyses favored MAPS, the effect was stronger in the as-treated analyses. It is possible that imputing virologic failure for all missing data was an overly conservative assumption. Yet, in all secondary analyses, changing the assumptions regarding missing data did not change the direction of the effect; that is, MAPS was the favored strategy in all results. Of course, dropouts diminish the cost-effectiveness of the intervention; limiting dropouts from care should be a priority for future refinements of MAPS. Fourth, we used microelectronic monitors to generate the feedback over the initial 3 months. The current cost of these monitors may render them out of reach for most patients and programs. Other objective techniques have been established for monitoring adherence (eg, pharmacy refill data^{4,21,40}); yet, it is unclear how they would perform if incorporated into MAPS instead of microelectronic monitors.

This study also has several particular strengths. The randomization, and the evident balance between the groups in most baseline characteristics, minimizes the likelihood that potential confounders biased the observed effect of MAPS. Second, fidelity to the manual of procedures always exceeded minimal standards. Third, the effect was present despite enrolling a population with many life challenges (ie, poverty, unemployment). Fourth, the effect was apparent in the face of a rigorous and very conservative analytic approach of considering loss to follow-up nonadherence; this stands in contrast to studies analyzing only those who remained in care.³¹ Fifth, the follow-up period extended for a full year, and there was no attenuation of the effect. Finally, unlike prior multimodal interventions, we have developed an implementation manual and workbook, which were used by the

staff in this study. Thus, MAPS has the potential to be implemented rapidly in settings where health behavior change expertise is unavailable.

In conclusion, MAPS improves pharmacotherapy adherence, although the benefit was somewhat diminished by dropouts. Since barriers to adherence and retention in care are similar, MAPS could be expanded to address retention in care as well; however, that remains to be evaluated. Since microelectronic monitors are not widely used in clinical practice, we believe MAPS should be refined to use other objective measures of adherence as the feedback tool. With the availability of the intervention manual, MAPS can be used immediately where the resources exist to implement it. Managed Problem Solving should also be adapted and tested in other treatment settings where adherence to oral pharmacotherapy is critical to health outcomes.

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Author Affiliations: Center for Clinical Epidemiology and Biostatistics (Drs Gross, Bellamy, and Strom and Mss Chapman and Han), Abramson Cancer Center (Drs Palmer and Coyne), Division of Infectious Diseases (Dr Gross and Ms O'Duor), Departments of Biostatistics and Epidemiology (Drs Gross, Bellamy, and Strom and Mss Chapman and Han) and Medicine (Dr Gross and Ms O'Duor), University of Pennsylvania Perelman School of Medicine, Philadelphia; Philadelphia Veterans Affairs Medical Center, Philadelphia (Dr Gross); Pennsylvania State University College of Medicine, Hershey (Dr Houts); and Health Psychology Section, Department of Health Sciences, University Medical Center, University of Groningen, Groningen, the Netherlands (Dr Coyne).

Correspondence: Robert Gross, MD, MSCE, Division of Infectious Diseases, Department of Medicine, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, 804 Blockley Hall, 423 Guardian Dr, Philadelphia, PA 19104-6021 (grossr@mail.med.upenn.edu).

Author Contributions: Dr Gross had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Gross, Palmer, Houts, Coyne, and Strom. *Acquisition of data:* Gross, Chapman, O'Duor, and Palmer. *Analysis and interpretation of data:* Gross, Bellamy, Han, Palmer, Houts, and Coyne. *Drafting of the manuscript:* Gross, Bellamy, Chapman, and Coyne. *Critical revision of the manuscript for important intellectual content:* Bellamy, Chapman, Han, O'Duor, Palmer, Houts, Coyne, and Strom. *Statistical analysis:* Gross, Bellamy, Han, and Houts. *Obtained funding:* Gross. *Administrative, technical, and material support:* Gross, Chapman, O'Duor, and Palmer. *Study supervision:* Chapman and Strom.

Conflict of Interest Disclosures: During the course of this study, Dr Gross received research support via contracts with Bristol-Myers Squibb and Abbott Laboratories for work related to HIV and its treatment, but not for work on this study. Dr Strom was supported in part by contracts with and received payment for consulting

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INVITED COMMENTARY

Lifetime HIV Antiretroviral Therapy Adherence Intervention

Timing Is Everything

Modern, potent antiretroviral therapy regimens can suppress human immunodeficiency virus (HIV) replication indefinitely. For those who have access to these drugs and who are able to adhere on a daily basis to these drugs, life expectancy now approaches that of individuals without HIV infection, particularly if they start therapy early.^{1,2} Full lifetime viral suppression offers the potentially transformative public health benefit of reducing transmission leading to a decline in number of new HIV infections.³

For many patients, however, adequate adherence to sustain viral suppression over a lifetime remains a major challenge. Antiretroviral adherence declines over time.⁴⁻⁶ Even

people with typically excellent adherence will experience treatment interruptions owing to inevitable disruptions in daily routine, relapse of substance use or mental illness, or simple pill fatigue. Interruptions of several days or more put patients at risk for virologic failure.^{7,8} As such, adherence support may be necessary for many, if not most, people at some time in the course of life-long treatment in order to achieve the full individual and public health impact of antiretroviral therapy.

Providing adherence support over a lifetime of antiretroviral therapy creates 2 major conundrums. First, most adherence interventions are time limited, and benefits do not typically last much beyond the cessation of the in-